UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,377	02/26/2002	Catherine Defrenne	BM45379	4141

38552 7590 01/25/2006

DECHERT LLP
P.O. BOX 10004
PALO ALTO, CA 94303-0961

EXAMINER	
BASKAR, PADMAVATHI	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,377	DEFRENNE ET AL.	
	Examiner	Art Unit	
	Padmavathi v. Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,27,29,31,32,35,40,41,43,48-,51 and 57-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,29,31,35,40,41,43,50--51 and 57-59* is/are rejected.

7)☒ Claim(s) *27,32,48 and 49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment

1. Applicant's amendment filed on 10/21/05 is acknowledged.

Status of Claims

2. Claims 25, 27, 29, 31, 32, 35, 40, 41, 43, and 48-51 have been amended.

Claims 52-56 have been canceled.

New claims 57-59 have been added.

Claims 25, 27, 29, 31, 32, 35, 40, 41, 43, 48-51 and 57-59 are under examination.

Claim Rejections-35 USC § 112 withdrawn

3. In view of cancellation of claim 54 and amendment to claims 51 and 40, the rejection under 35 U.S.C. 112, second paragraph is withdrawn.

Claim Rejection - 35 U.S. C. 112, first paragraph maintained

4. The rejection of claims 25, 29, 31, 35, 40, 41, 43, 50-51 and newly added claims 57-59 is maintained as set forth in the previous office action under 35 U.5.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising the amino acid sequence SEQ ID NO: 2, said polypeptide is a recombinant polypeptide, a fusion protein comprising the amino acid sequence SEQ.ID.NO: 2, an immunogenic composition comprising the amino acid sequence SEQ.ID.NO: 2 and a pharmaceutically acceptable carrier, an isolated polypeptide consisting of an immunogenic fragment sequence of 15 or 20 amino acids of SEQ.ID.NO: 2 does not reasonably provide enablement for a polypeptide comprising an immunogenic fragment sequence of at least 15 or 20 amino acids of SEQ.ID.NO: 2, where in the immunogenic fragment , when administered to a subject in a suitable composition which can include an adjuvant, or suitable carrier coupled to the polypeptide, induces an antibody or T-cell

response that recognizes the polypeptide SEQ.ID.NO: 2 is maintained as set forth in the previous office action.

The claims are drawn to an isolated polypeptide and a method for inducing an immune response comprising a member selected from the group consisting of (a) the amino acid sequence SEQ.ID.NO: 2; (b) an immunogenic fragment comprising at least 15 or 20 (the examiner is considering these as fragments) contiguous amino acids of SEQ.ID.NO: 2, where in the isolated polypeptide, when administered to a subject in a suitable composition which can include an adjuvant, or suitable carrier coupled to the polypeptide, induces an antibody or T-cell response that recognizes the polypeptide SEQ.ID.NO: 2. Claims are also drawn to a recombinant polypeptide comprising the amino acid sequence SEQ.ID.NO: 2 and fragments of said polypeptide.

The instant claims are evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the disclosed invention is an isolated polypeptide of SEQ ID NO: 2 from *Neisseria mengitidis* ATCC 13090 strain which is designated as a " BASB082" polypeptide in examples 1-5. The specification teaches that this polypeptide has been obtained by recombinant cloning and contains 758 amino acids. However, the specification is silent in disclosing whether this polypeptide recognizes antibodies that are obtained from Neisseria infected individuals. Further, the specification fails to indicate or teach any description of fragments of said polypeptide that are able to bind to antisera raised against full-length polypeptide and provides no working examples demonstrating (i.e., guidance) enablement for any *fragments and* uses of the claimed polypeptide.

The state of the prior art indicates that protein chemistry is probably one of the most unpredictable areas of biotechnology and is highly complex. As taught by the prior art (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6), the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis. The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67) teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis

which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition.

In addition to the art-recognized unpredictability, the specification has not provided any guidance as to how an artisan would have fragments that have functional properties in immunological recognition. The specification, however, provides no guidance demonstrating enablement for making and using the claimed fragments. Thus, making and using fragments of a polypeptide must be considered highly unpredictable, requiring a specific demonstration. Absent such demonstration, the skilled artisan would be forced into undue experimentation to make and use the invention commensurate in scope with these claims.

Applicants' arguments filed on 10/21/05 have been fully considered but they are not deemed to be persuasive.

Applicant ' states that the examiner does not question the **immunogenicity** of the BASB082 fragments itself. Applicant now provides another set of Exhibits A-J (published journal articles) relating to various short peptides that were used to generate antibodies.

The examiner has replied to applicants arguments in the previous Office action with respect to Exhibits filed in the previous amendment. The examiner has reviewed the exhibits A-D relating to synthetic peptides and E (use of peptide to probe viral antigen for specific epitope) F and G (vaccine related to class 1 membrane protein) H and I (related to protein molecular weight calculator and computer tools) J (accession number for outermembrane for MC 58 strain) understands that short peptides consisting of 6 or 7 or 8 amino acids have been used to raise antibodies and for epitope mapping. However, the examiner is not stating that synthetic peptides can not be used for raising antibodies etc or for mapping epitopes but fragments as claimed (i.e., fragment **comprising** of at least 15 or 20 contiguous amino acids of SEQ.ID.NO: 2) are not supported by the present specification because the limitation "comprising" leaves " the claim open for the inclusion of unspecified ingredients even in major amounts and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. Therefore, the

claimed immunogenic fragment having 15 or 20 amino acids plus unlimited amino acids result in an unknown peptide without structural and functional properties Therefore, the antibodies raised against broadly claimed fragments have not shown to be recognizing either the full-length protein or reactive to fragments consisting of 15 or 20 amino acid peptides. Hence examiner's concern regarding the language used is important in claiming immunogenic fragments. . Please note the exhibits submitted by the applicant also indicate peptides consists only 10 or 15 contiguous amino acids and nothing else.

Evidentiary references as provided by the applicant clearly indicated the use of short 12 –20 mer peptide (i.e., fragment **consisting** of 15/20 contiguous amino acid sequence of SEQ.ID.NO: 2) with carrier protein are used to raise antibodies and those antibodies have been shown to be binding to full length protein often (for example any one of exhibits A-D). However, applicant is not claiming fragments consisting of 15 or 20 amino acids of SEQ.ID.NO: 2 but claiming fragment **comprising** of at least 15 or 20 contiguous amino acids of SEQ.ID.NO: 2 and such fragments have not been shown to be reactive to antibodies raised against either full length protein, BASB082 or positive sera from patients to reveal immunodominant regions of the antigen BASB082.

Further, applicant states that examiner did not provide evidence to demonstrate loss of immunogenicity of such operable species when situated within a recombinant protein.

The examiner again would like to bring applicant's attention to the claim language used in claiming fragments. As it is known in the art of immunology (see right column page 3265 of Arnon et al FASEB J. 1992 Nov; 6(14): 3265-74) continuous epitopes are short linear peptide fragments of **the antigen** that is able to bind to antibodies raised against the intact protein. However, the fragments as claimed are not the fragments of BASB082 (i.e. an isolated polypeptide consisting of 15 or 20-----.) but claiming very broad peptides (.e. an isolated

polypeptide comprising 15 or 20---) that have no structure and function as discussed above in the rejection. The specification does not teach that the fragments as claimed having specificity to N.meningitidis antigen BASB082.

As discussed in the previous office action, for example Molloy et al (Molecular Immunol. 35, 1998, pages 73-81) teach, production of TCR (TCR comprising two other immunoglobulin super family member proteins) epitope has remained problematic as the majority of the recombinant proteins remain insoluble and are not processed. Therefore, the claimed isolated recombinant polypeptide comprising an immunogenic fragment of at least 15 or 20 contiguous amino acids of SEQ.ID.NO: 2 (immunogenic fragment without a structure) for mapping t-cell epitopes must be considered highly unpredictable requiring a specific demonstration of efficacy of the polypeptide in mapping epitopes. Absent such demonstration, the invention would require undue experimentation to practice as claimed.

Claim Rejections - 35 USC 102 maintained.

5. The rejection of claims 25, 29, 31, 35, 40, 41, 43, 50-51 and newly added claims 57-59 under 35 U.S.C. 102(a) as being anticipated by Wedege et al Infect Immun. 1998 Jul; 66(7): 3223-31 is maintained as set forth in the previous office action.

Wedege et al disclose a vaccine comprising outermembrane vesicles (OMV) isolated from vaccine strains 44/76 as antigen (see page 3224, left column, second paragraph under Immunoblotting). The prior art also discloses a recombinant Pore OMV vaccine (see 3226, left column, under 80-70kDantigens). After electro transfer, the OMV proteins from these two vaccine preparations were blotted with serum obtained from vaccinated individuals. Table 2 shows an isolated polypeptide 80kD antigen reacted with IgG antibodies obtained from sera taken from individuals after immunization. The 80kD antigen from OMV vaccine reads on claims 25, 31, and 35 because the art discloses a vaccine OMV comprises 80kD antigen which appears to be similar to the claimed product polypeptide. Therefore, it is inherent that the 80 kD OMV antigen comprises the claimed polypeptide and immunogenic fragments as claimed in 25, 31, 35 because characteristics such as amino acid sequence SEQ.ID.NO: 2 is inherent in the preparation of vaccine comprising isolated polypeptide 80kD OMV vaccine and thus read on the claimed invention including immunogenic composition (claims 40, 41) and a method for inducing an immune response (claim 43) because vaccine is given to human volunteers and the sera obtained after vaccine reacted with 80kD antigen (see Table 2) and thus it elicits the

production of antibody IgG etc (see page 3225, right column through page 3226). The isolated antigen 80 kD meet the limitations of the claims 25, 27, 31, 35 because the broadly claimed polypeptide having 758 amino acids is equivalent to 80 kD of the prior art disclosed protein since each amino acid molecular weight is 110 daltons. When producing OMV vaccine, the composition would inherently contain more than one polypeptide (fusion proteins) and a carrier present, i.e., buffer for pharmaceutical use as required by claims 35 and 40. Therefore, the composition comprising an isolated 80 kD polypeptide in buffer read on immunogenic composition of the claimed invention. Since vaccine comprises more than one antigen it reads on the claim 43.

The prior art also discloses recombinant PorA OMV vaccine (see page 3226, left column under 80-70kD antigen), which contains 80kD antigen (see table 2) and thus reads the recombinant polypeptide, immunogenic composition comprising SEQ.ID.NO: 2 and a fusion protein comprising said polypeptide as claimed in claims 50-51 and 57 –59 for the same reasons as discussed above.

In the absence of evidence to the contrary the disclosed prior art OMV vaccine, recombinant PorA vaccine and composition comprising said protein and the claimed polypeptide and immunogenic composition are the same. Since the Office does not have the facilities for examining and comparing applicants' claimed isolated immunogenic polypeptide comprising a polypeptide comprising an amino acid sequence SEQ.ID.NO: 2, composition comprising said polypeptide with the 80kD protein and composition comprising said protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed isolated or recombinant immunogenic polypeptide, vaccine composition comprising said polypeptide and 80kD protein and composition of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicants' arguments filed on 10/21/05 have been fully considered but they are not deemed to be persuasive.

Applicant states that the vaccine disclosed in the prior art is from serogroup B strain and contains whole antigenic mosaic of the meningococcal outer membrane in the vaccine. Briefly, the vaccine was prepared "by fermentation growth and extraction of the bacteria with the detergent deoxycholate, contains about 8% phospholipid, 7% lipopolysaccharide and 16% deoxycholate etc. The Wedege study demonstrates that the 80 kD protein, [illegible], is present at 3% or less of total protein. Beyond its estimated size, its presence in outer membrane vesicle preparations, and its immunogenicity, nothing more is known about the 80 kDa protein. As rejected, applicants' claims 25, 29 and 31 had been drawn to "an isolated polypeptide. Further applicant states that 'A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. Moreover, a prior art reference may

anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.

The examiner disagrees with the applicant because applicant is arguing the limitations such as "by fermentation growth and extraction of the bacteria with the detergent deoxycholate, contains about 8% phospholipid, 7% lipopolysaccharide and 16% deoxycholate etc are not set forth in the claims. Further, the arguments " 80 kD protein is present at 3% or less of total protein" etc are again not correct, as the present claims do not set forth such limitations. With respect to the argument that it is not an isolated protein, please note the 80kD protein is isolated from outer membranes from sero group B strain.

Claims 27, 32, 48-49 have not been rejected. However, claims 25, 29, 31, 35, 40, 41, 43, 50-51 and 57-59 have been rejected because of open claim language. Therefore, the disclosed protein comprises fragments of SEQ.ID.NO: 2 as claimed fragments do not set forth clear structural boundaries. Further applicant's arguments that PorA is not BASB082 and it is, not the same strain are again considered as limitations that are not set forth in the claims. Therefore, the prior art rejection is maintained.

Remarks

6 Claims 25, 29, 31, 35, 40, 41, 43, 50-51 and 57-59 stand rejected.

Claims 27, 32, 48 and 49 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action

8. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature

or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Padma Baskar Ph.D.